A 41

# PATENT ABSTRACTS OF JAPAN

(11)Publication number : **07-100191**

(43)Date of publication of application : **18.04.1995**

(51)Int.Cl. **A61J 3/08**
**A61K 9/02**

(21)Application number : **05-272935**

(22)Date of filing : **06.10.1993**

(71)Applicant : **DAIKYO YAKUHIN KOGYO KK**

(72)Inventor : **MACHIDA RYOJI**
**IWATA MASANORI**
**NAGAI TSUNEJI**

## (54) SUSTAINED RELEASE SUPPOSITORY

(57)Abstract:

PURPOSE: To provide a sustained release suppository to be applied to an anus, vagina, etc., capable of gradually releasing the medicinal component by using a hot-melt mixture of Witepsol with an ethylene-vinyl acetate copolymer as a base.

CONSTITUTION: This sustained release suppository comprises as the base a hot-melt mixture of Witepsol with an ethylene-vinyl acetate copolymer. To this fused mixture, polyethylene glycol(PEG) is added as release adjusting agent. Also, verapamil hydrochloride or progesterone is added as active ingredient to the hot-melt mixture. By using the base, it becomes possible to obtain the intensity enough to avoid the melting by body temperature and sustained releasability of medicines. This base can be stored even if not in a cool place. Further, it becomes possible to control the amount of releasing active ingredient by adjusting the amount of adding PEG when PEG is added as releasing adjusting agent.

LEGAL STATUS

[Date of request for examination] 21.09.2000

[Date of sending the examiner's decision of rejection] 20.05.2003

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of

rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

CLAIMS

---

[Claim(s)]
[Claim 1] Sustained-release suppository characterized by making fusion mixture of witepsol and an ethylene-vinyl acetate copolymer into a basis.
[Claim 2] Sustained-release suppository according to claim 1 characterized by adding a polyethylene glycol as an emission regulator into the fusion mixture of said witepsol and ethylene-vinyl acetate copolymer.
[Claim 3] Sustained-release suppository according to claim 1 characterized by adding verapamil hydrochloride as an active principle into the fusion mixture of said witepsol and ethylene-vinyl acetate copolymer.
[Claim 4] Sustained-release suppository according to claim 1 characterized by adding progesterone as an active principle into the fusion mixture of said witepsol and ethylene-vinyl acetate copolymer.

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

DETAILED DESCRIPTION

---

[Detailed Description of the Invention]
[0001]
[Industrial Application] About the suppositories applied to the anus or a vagina, especially, this invention does not have to carry out cool place preservation, and relates to suppositories equipped with sustained-release.
[0002]
[Description of the Prior Art] Usually, suppositories are solid external preparations which mix with a basis equally, cast drugs in a fixed configuration, and apply them to the anus or a vagina, and are external preparations of a half-solid applied to coelomata other than the oral cavity.
[0003] Generally, although suppositories had many things aiming at the local action to hemorrhoids etc., recently, suppositories aiming at a systemic action are increasing. Generally, rectal suppositories are carrying out the cone form or the spindle shape, and although weight 1-3g, die length of 3-4cm, and pessaries are weight 2-4g in a globular form or an ovoid, various advanced types are proposed after that. Amelioration of a configuration is easy to insert, if it inserts, it is hard to jump out and a form which is well stuck to the affected part after insertion is once searched for.
[0004] It roughly divides into suppositories, there are basis form suppositories which blend a drug effect component, an additive, etc. into a basis, and gelatine capsule suppositories which made the gelatine capsule include a paste-like drug solution as them, and basis form suppositories are common.
[0005] It is divided into oleaginous bases, emulsion bases, and water-soluble bases, and as conditions which must be provided as a basis, it melts according to temperature, or softens, or the suppository base of basis form suppositories melts gradually with secretion liquid. Usually, cacao butter, glycerogelatin, macro gall, witepsol, etc. are used as a basis.
[0006] Moreover, if a surfactant is good to emulsion bases, in order that it may close the solubility to the basis of a chief remedy component, and diffusibility to them among basis form suppositories, it may be added by the basis if needed. However, since absorption of a drug may be checked by combination of a surfactant depending on the case, cautions are required.
[0007]
[Problem(s) to be Solved by the Invention] By the way, the thing aiming at a systemic action is increasing suppositories as mentioned above, and membrane, such as the rectum which is the main application site, or a vagina, is being improved as a route of administration of a drug. A drug delivery system (DDS) attracts attention from viewpoints, such as the effectiveness of drugs, and safety, in recent years, and many new controlled release pharmaceutical preparation has been developed by the device of dosage forms etc. It doubles with the application purpose also about suppositories, and emission adjustment is being required.
[0008] On the other hand, verapamil hydrochloride is a calcium antagonist, it is administered orally, controls an inflow into the muscle cell of calcium ion (calcium2+), decreases peripheral vascular resistance, and is used for the therapy of angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and myocardial infarction.
[0009] moreover, the corpus-luteum function which progesterone (PRG) causes a failure to formation of pregnancy, and maintenance, and causes infertility, ******, a miscarriage, and a premature delivery -- administration is performed every day by intramuscular injection as an insufficient remedy.
[0010] However, there were problems, such as blood-drug-concentration maintenance by the lapse of the drug effect by the decomposition in the burden to digestive organs, such as the stomach, liver, etc., as a side effect of internal use medicine. Moreover, since self-administration is impossible for intramuscular injection, as for the burden to a patient, it is still larger that there is the need for hospitalization or going to hospital regularly, to be accompanied by the pain, etc.

[0011] In order to compensate the fault of pharmaceutical preparation, such as these internal use medicine and intramuscular injection medicine, current expectation of the development of the pharmaceutical preparation in which self-administration and blood-drug-concentration maintenance are possible is carried out.
[0012] This invention aims at obtaining suppositories equipped with sustained-release [ which can emit a drug effect component gradually ], and obtaining suppositories equipped with sustained-release [ which can adjust the burst size per time amount ].
[0013]
[Means for Solving the Problem] The sustained-release suppository concerning invention of claim 1 makes a basis fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0014] Moreover, the sustained-release suppository concerning invention of claim 2 adds a polyethylene glycol as an emission regulator into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0015] Furthermore, the sustained-release suppository concerning invention of claim 3 adds verapamil hydrochloride as an active principle into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0016] Moreover, the sustained-release suppository concerning invention of claim 4 adds progesterone as an active principle into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0017]
[Function] Although the witepsol (Witepsol) conventionally used as a suppository base was quickly dissolved in temperature and the drug was emitted, it was found out in what added the ethylene-vinyl acetate copolymer (it is hereafter described as EVA), and was made into the mixed base agent that sustained-release [ good ] is shown.
[0018] Therefore, the reinforcement which is not dissolved is obtained according to temperature and sustained-release [ of drug release ] is possible for what made the basis fusion mixture of the witepsol of this invention, and EVA. Furthermore, even if not saved specially in a cool place, it can save.
[0019] Moreover, since a burst size increases according to the addition of PEG, what added the polyethylene glycol (it is hereafter described as PEG) as an emission regulator into the fusion mixture of the witepsol of this invention and EVA can control the burst size of an active principle by controlling the addition of PEG.
[0020] There are various drugs, hormone, etc. as an active principle added by the fusion mixture of witepsol and EVA. To be the drugs, hormone, etc. with which a living body is medicated especially with time, and what is necessary is just the drugs, hormone, etc. by which membrane absorption is moreover carried out from the rectum or a vagina wall.
[0021] since especially the thing that added verapamil hydrochloride as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and the verapamil hydrochloride used for the therapy of myocardial infarction -- the inside of the body -- a basis -- softening -- gradually -- gelling -- ** -- the verapamil hydrochloride which is not can be gradually prescribed for the patient to the living body.
[0022] Especially in the thing which contains verapamil hydrochloride as an active principle, by using for the witepsol 4 section the basis which added PEG 30% to the fusion mixed base agent of the EVA1 section, the long time of the 1st day or more can be covered, and emission can be maintained.
[0023] Furthermore, since what added progesterone as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis the progesterone which is one of the hormone aiming at the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery, it can be followed on a basis softening and gelling gradually, and can prescribe progesterone for the patient gradually to the living body.
[0024]
[Example]
Verapamil hydrochloride (a sigma company and Lot.70H0897) was used as an example 1. verapamil hydrochloride sustained-release suppository 1 sample chief remedy. As a basis of suppositories, witepsol W-35 and an ethylene-vinyl acetate copolymer (it is hereafter described as EVA) 150,250,420 were used.
[0025] 2) the mixing ratio of the selection witepsol W-35 of optimal EVA, and each of EVA150,250,420 -- 2:1, 3:1, and 4: -- about the basis which carried out fusion mixing as 1 and 6:1, the reinforcement in 25 degrees C and the viscoelasticity in 37 degrees C were measured using the visco-elastic meter (the trade name "FUDOW rheometer" immobilization industrial incorporated company make, model NRM-2002 D-D), and optimal EVA was chosen.
[0026] 2-1) The reinforcement of a basis was measured supposing the handling in the measurement ordinary temperature of the reinforcement in 25 degree C. Drawing 1 is the explanatory view of the adapter of the wedge used for measurement of the reinforcement of a basis. The reinforcement of the basis prepared in 5mm in thickness and width of face of 10mm was measured as shown in drawing. Drawing 2 is the diagram showing the relation between the mixing ratio of EVA in the basis in 25 degrees C, and reinforcement. In drawing, an axis of ordinate shows

reinforcement (kg) and an axis of abscissa shows the mixed concentration (%) of EVA.
[0027] The mixed ratio of three kinds of EVA was changed, the mixed dissolution was carried out with witepsol, and the reinforcement of each basis in 25 degrees C was measured as shown in drawing. The level dotted line in drawing shows the reinforcement at the time of witepsol independent. Since suppositories needed to have reinforcement sufficient in ordinary temperature (15-25 degrees C), they were understood that EVA 150 and 250 is the more nearly optimal than drawing.
[0028] 2-2) The viscoelasticity of the basis in 37 degrees C was measured supposing the time of the measurement intrarectal administration of the viscoelasticity in 37 degree C. Drawing 3 is the explanatory view of the adapter for measuring the viscoelasticity of a basis. The viscoelasticity of the basis of the one-side shape of a 10mm cube dipped in the 37-degree C hot bath for 5 minutes was measured using the adapter of a disk form (diameter of 7mm) as shown in drawing.
[0029] Drawing 4 is the diagram showing the relation between the mixing ratio of EVA in the basis in 37 degrees C, and viscoelasticity. In drawing, an axis of ordinate shows visco-elastic degree (kg), and an axis of abscissa shows the mixed concentration (%) of EVA. Change of the elasticity by addition of EVA did not not much have any EVA as shown in drawing.
[0030] In addition, since flexibility was searched for in order to avoid foreign body sensation after insertion of suppositories, in 25%, most flexible EVA250 was chosen by subsequent preparation. Moreover, this basis can maintain the cubical original form, without fusing during heating by hot bath. Therefore, compared with the conventional suppositories, even if it does not carry out cool place preservation, it can fully save.
[0031] 3) the method-of-preparation witepsol W-35 and EVA250 of verapamil hydrochloride sustained-release suppository -- 3:1 and 4: -- verapamil hydrochloride sustained-release suppository was prepared with the fusion method using the basis mixed by 1 and 6:1. It was made to contain 60mg of verapamil hydrochloride in per suppositories at this time.
[0032] After the concrete method of preparation put witepsol W-35 and EVA250 into the beaker, covered on the lap for the food packing made from a polyvinylidene chloride first and carried out the nitrogen purge of the internal air, it was heated for 7 minutes and 30 seconds with the microwave oven. Next, it mixed until it put on the hot plate and became homogeneity using the glass rod so that the temperature of a basis might not fall. After being easy to add verapamil hydrochloride and stirring it to the basis which became homogeneity, it slushed into the metal suppository mold and suppositories (about 1.42g per piece) were prepared.
[0033] 4) It asked for the elution nature of the drug from the elution test suppositories of verapamil hydrochloride sustained-release suppository by ** cylindrical paper filter sampling and the ** basket bead method for having changed the JP rotatory basket method. It carried out using the tester ( model NTR-VS3 by Toyama industrial incorporated company) at rotational-speed 150rpm, the testing-liquid physiological saline of 900ml, and the solution temperature of 37**0.5 degrees C.
[0034] 4-1) Cylindrical-paper-filter-sampling drawing 5 is the explanatory view showing the outline of cylindrical paper filter sampling. The basket (51) used the thing with a diameter [ of 20mm ], and a depth of 30mm used with the JP rotatory basket method as shown in drawing. The extraction thimble (52), and (the Tokyo filter paper firm make, No.84 and the diameter of 20mm) were put in into the basket (51), a physiological saline (54) and suppositories (50) were put in into it, the lid made of silicone rubber (53), and (the thickness of 4mm and the diameter of 18mm) were carried out, and the tester was made to attach and rotate this. 0. 5ml of samples was extracted 5, 1, 3, and 5 or 24 hours after, and the physiological saline of tales doses was filled up.
[0035] 4-2) Using the spectrophotometer (the Jasco Industries make, Ubest-30 mold), the absorbance [ in / for the amount of verapamil hydrochloride to which elution of / in the quantum extraction sample of verapamil / was carried out / 229nm ] was measured, and it computed from the calibration curve (correlation coefficient 1.000) created beforehand. The regression is as follows.
Concentration (mug/ml) = 32.09x absorbance +0.225 [0036] 4-3) Emission nature (1) drawing 6 of verapamil hydrochloride sustained-release suppository is the diagram having shown the result of the emission nature of the drug from the suppositories by cylindrical paper filter sampling. In drawing, an axis of abscissa shows time amount for the rate (rate of emission) (%) to the content of the amount of verapamil hydrochloride to which elution of the axis of ordinate was carried out. This drawing showed that a basis showed sustained-release [ remarkable ] over 24 hours in all ratios.
[0037] Moreover, it turned out that emission nature increases, so that the mixing ratio of witepsol became large. However, the peak price was also 8% (1 or 24 hours after ratio 6:), and that of the rate of drug release 24 hours after a mixed base agent was extremely low as pharmaceutical preparation of verapamil hydrochloride.

[0038] 4-4) Emission nature (2) which is verapamil hydrochloride sustained-release suppository In order to improve elution nature, the polyethylene glycol (it is hereafter described as PEG) 6000 which is a water soluble polymer was added 30% there to the basis which carried out fusion mixing of witepsol W-35 and EVA250 by 4:1. Drawing 7 is the diagram having shown the result of the emission nature of the drug at the time of adding PEG. In drawing, an axis of abscissa shows time amount for the rate of emission of the verapamil hydrochloride to which elution of the axis of ordinate was carried out (%).
[0039] In the case of the ratio 4:1, emission was promoted for 5.4% to 10.4% as shown in drawing. in addition -- the case where PEG is similarly added 30% although not shown in drawing -- the case of a ratio 3:1 -- 2.9% -- 6.6% -- the case of a ratio 6:1 -- 7.6% -- 12.0% -- ** -- the rate of emission was promoted for any ratio about twice [ about ].
[0040] 4-5) In the body, supposing a pressure being applied to suppositories, it examined to the basket bead method pan using the basket bead method per PEG addition suppositories, and the comparison with cylindrical paper filter sampling was performed to it. Drawing 8 is the explanatory view showing the outline of the basket bead method.
[0041] The basket (81) used the thing with a diameter [ of 40mm ], and a depth of 20mm. Suppositories (80) were installed in the horizontal location, two kinds of 30 beads (the product made of nylon, diameter of 3.95mm) were used together, and the bead (83) of B type which sinks the bead (82) of A type which floats in a basket into a physiological saline (84) in 30 pieces (the product made from polypropylene, diameter of 3.95mm) and a basket was performed.
[0042] 5ml of samples was extracted that it is the same as that of cylindrical paper filter sampling, 0.5, 1 and 3, and 5 or 24 hours after, and the physiological saline of tales doses was filled up. Moreover, the quantum of the amount of verapamil hydrochloride to which elution of [ in an extraction sample ] was carried out as well as the above-mentioned was performed.
[0043] Drawing 9 is the diagram having shown the result of the emission nature of the drug of the PEG addition suppositories of cylindrical paper filter sampling and the basket bead method. In drawing, an axis of abscissa shows time amount for the verapamil hydrochloride concentration (emission concentration) (%) to which elution of the axis of ordinate was carried out. Maintaining sustained-release [ which was stabilized by any suppositories of a ratio over 24 hours ] was checked as shown in drawing.
[0044] Moreover, the emission nature in the basket bead method was higher than cylindrical paper filter sampling, and it went up by 4:1 and it went up even to 22.4% by 6:1 26.5% 17.8% by the ratio 3:1. As mentioned above, when adding PEG to the witepsol-EVA basis, it was checked that a burst size is controllable. Therefore, it is thought in accordance with the therapy concentration of various drugs that application is fully effective.
[0045] 5) From the result of the verapamil hydrochloride sustained-release suppository administration experiment elution test to a rabbit, the rabbit was medicated with the verapamil hydrochloride addition suppositories which added PEG 30% to witepsol-EVA mixed stock (4:1), and the absorption experiment by the rabbit was conducted. The amount of suppositories Nakashio acid verapamil was prepared so that 60mg per piece might be contained as well as an elution test. In addition, what added the verapamil hydrochloride of tales doses was prepared for the witepsol independent basis as a comparison.
[0046] Intrarectal administration of the verapamil hydrochloride addition suppositories was specifically carried out to the feminity Japan white rabbit (one groups [ three ]) with a weight of 2.9-3.2kg made to abstain from food for 24 hours, and about 50microl extraction of blood was done from the lug vein 1, 3, and 5 or 24 hours after. The blood drug concentration of the extracted blood was measured using high speed liquid chromatography.
[0047] The measuring method added internal standard matter solution (parahydroxybenzoic acid 2 ethylhexyl methanol solution) 100microl and methanol 200microl to 100micro of blood serums l, applied them to the centrifugal separation machine, performed the deproteinization, and made digestive liquor the sample solution. The device and conditions of high speed liquid chromatography are as follows.
[0048] Pump Shimadzu LC-3A detector Shimadzu The SPD-6A rate of flow 1.0 ml/min column YMC-Pack ODS 150x4.6mmI.D
Mobile phase Phosphate buffer solution: Excitation wavelength of methanol =1:4 detector 278nm [0049] The amount of verapamil hydrochloride was computed by the calibration curve (correlation coefficient 0.9961) created beforehand. The tropic is as follows.
Peak area ratio = 1.5493+9.302x10-3xX (ng/ml)
[0050] Drawing 10 is the diagram showing change of the blood drug concentration of the verapamil hydrochloride when prescribing for the patient the verapamil hydrochloride suppositories which consist of a witepsol independent basis. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, and an axis of abscissa shows time amount. In addition, the doses to Rabbits A, B, and C are 21.7, 19.0, and 21.0 mg/kg, respectively.

[0051] In the witepsol independent used as a suppository base from the former, the transient absorption profile was shown and sustained-release was not accepted as shown in drawing 10 . Cmax in Rabbits A, B, and C They were 195.9 and 129.9 or 199.5mg/ml. In addition, the blood drug concentration of 24 hours high to the abnormalities in Rabbit C is considered to be a certain experiment mistake.
[0052] Drawing 11 is the diagram showing change of the blood drug concentration of the verapamil hydrochloride when medicating a witepsol-EVA mixed base agent (4:1) with the verapamil hydrochloride addition suppositories which added PEG 30%. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, and an axis of abscissa shows time amount.
[0053] In witepsol suppositories, it turns out that the time amount (Tmax) which reaches the maximum drug concentration which was 30min is behind to an average of 3.5 hr(s), or that there is an inclination to maintain higher blood drug concentration 24 hours after as shown in drawing 11 .
[0054] Drawing 12 is the diagram which computed drawing 10 , and averages and standard deviation of 11. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, an axis of abscissa shows time amount, and each plot is the average and standard deviation of each rabbits A, B, and C. It turns out that sustained-release [ Tsuguaki suppositories / using the new basis of this invention shown in drawing 11 ] is shown by drawing 12 . Although it cannot necessarily say that this emission profile is suitable as verapamil hydrochloride pharmaceutical preparation, it is thought that the flexibility in the reinforcement and temperature of these suppositories, firmness, and sustained-release are applicable also to a drug besides future.
[0055] As mentioned above, the following knowledge was acquired as a result of trying the application to the sustained-release suppository by the new basis obtained from the former by carrying out fusion mixing of EVA by the witepsol used as a suppository base.
[0056] In ordinary temperature, since the witepsol-EVA mixed base agent prepared by this example was harder than a witepsol independent, and was not dissolved by temperature but showed moderate flexibility, it also united the sustained-release field and was considered to be useful. Moreover, it succeeded in raising the rate of emission, maintaining sustained-release by adding PEG to a basis in an elution test. When the result of these in vitro experiments was applied to the in vivo experiment using a rabbit, the result which suggests sustained-release similarly was obtained.

[0057] In this example, although verapamil hydrochloride was used as a drug, even if changed into other drugs, it was surmised that it could acquire sustained-release. The property of maintaining emission especially over the long duration of the 1st day or more is very useful also to development of the pessary which uses hormone etc. as a chief remedy.
[0058] Progesterone was used as an example 2. progesterone suppositories 1 sample chief remedy. Witepsol W-35 and five kinds of EVA (EVA-40Y, 45X, 150,250,420) were used as a basis of suppositories. Moreover, all of reagents, such as other ethanol, used the best article.
[0059] 2) Progesterone content sustained-release suppository was prepared for this with scorification using the basis which mixed the preparation witepsol and EVA of progesterone sustained-release suppository at a rate of 9:1. In addition, the progesterone content suppositories which added progesterone to the witepsol W-35 independent basis were prepared with scorification as control. The amount of progesterone in suppositories set all to 100mg.
[0060] 3) it asked for the elution test of the elution test profit **** sustained-release suppository of progesterone sustained-release suppository by the new emission examining method. As an emission tester, the JP elution test machine (made in the Toyama factory) was used. Drawing 13 is the explanatory view showing the outline of an emission tester. as being shown in drawing -- rotation shaft (131) **** -- propeller (132) it attaches -- having -- further -- rotation shaft (131) Basket (133) surrounded with the network at the tip It is attached.
[0061] It equips with an extraction thimble (the Toyo Roshi Kaisha, Ltd. make, No.84, 20x90mm) (134) into a basket, and is a bead (135) made from plastics with a diameter of 4mm in this. Witepsol suppositories (136) Propeller after putting in and covering with the lid made from silicon (132) Rotation shaft (131) It was made to rotate.
[0062] test fluid (137) ****** -- 5ml of reagents was extracted with time using 900ml of ethanol ********** 30%, and 30% ethanol ********** of tales doses was filled up. The number of beads put in in an extraction thimble was examined by making it change with 50 - 150rpm in the rotational frequency of 0-60 pieces and a basket.
[0063] Using the absorptiometer (the Jasco Industries make, Ubcst-30 mold), the quantum of progesterone measured the absorbance [ in / for test fluid / the wavelength of 248nm ], and asked for it using the calibration curve (y=16.8831x+0.145114 r=0.999839) created beforehand.
[0064] 3-1) Temperature drawing 14 of a physiological saline is the diagram showing the difference of the emission nature of progesterone in case temperature is different. In drawing, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate was eluted. 30 beads were put in with the witepsol

suppositories which contain 100mg of progesterone in an extraction thimble 30%, using 900mg of ethanol ********** as test fluid, and it carried out by rotational frequency 150rpm. Temperature was performed at 36 and 37 or 38 degrees C, and compared the emission nature of progesterone.

[0065] Although, as for the burst size of the progesterone 5 hours after emission test initiation, the difference was seldom seen in 37 degrees C and 38 degrees C, in 36 degrees C, the burst size decreased extremely, as shown in drawing.

[0066] From the above result, it is thought in the emission trial of these suppositories that the effect of temperature, i.e., fusion of a basis, influences a burst size greatly. Therefore, temperature of the test fluid in a consecutive trial was made into 37.5**0.5 degrees C near rectal temperature.

[0067] 3-2) The number of beads and engine-speed drawing 15 are the diagrams showing the difference of emission nature in case the number of beads added in an extraction thimble and the engine speed of a basket are different, and, as for 50rpm and drawing b, the engine speed of a basket shows the case of 150rpm for drawing a, as for 100rpm and drawing c. Moreover, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate of each drawing was eluted.

[0068] The number of beads added in an extraction thimble specifically changed the rotational frequency of 0, 10, 30 or 60 pieces, and a basket with 50,100,150rpm, and the emission trial was performed. When engine speeds were 50 and 100rpm as shown in drawing, the effect to the burst size of the number of bead addition was not seen. On the other hand. In 150rpm, the difference was looked at by the burst size with the number of bead addition, and the 30-bead burst size was 78.3%.

[0069] Drawing 16 is the diagram which computed the emission area under the curve (ADT) and the average emission rate (MDT) from the result of drawing 15 , drawing a is an emission area under the curve (ADT), and drawing b is an average emission rate (MDT). In drawing, an axis of ordinate shows an emission area under the curve (ADT) and an average emission rate (MDT), and the axis of abscissa shows the number of beads.

[0070] although ADT showed the peak price in 30 beads as shown in drawing -- MDT -- bead additive-free -- setting -- a high value -- that is, it emitted slowly. Moreover, although emission became quick by addition of a bead, the difference between the numbers of a bead was seldom seen. This is raising an engine speed, and in order for a bead to stir and to make it dissolve more quickly than a basis, it is considered that emission of progesterone becomes quick.

[0071] However, when 60 beads were put in in an extraction thimble, even if it raised the rotational frequency to 150rpm, the burst size did not increase. The movement space of a bead will become narrow and this will be considered because it becomes impossible to contribute to the dissolution of suppositories, and stirring not much, if suppositories and 60 beads are put in into an extraction thimble.

[0072] From the above result, it became clear by the new emission examining method for having used the above-mentioned JP elution test machine that it is good to carry out by 30 bead additions in an extraction thimble and rotational frequency 150rpm of a basket. leakage and Muranishi of a basis [ like a rotatory basket method ] whose emission examining method of this is -- it is the approach of compensating a fault, like the repeatability in law is inferior, and since the JP elution test machine is used, it is thought that it is cheaper than the rotation dialysis cel method.

[0073] 4) The basis which mixed respectively the measurement witepsol of endoergic peak temperature and the amount of endoergic and five kinds of EVA to 9:1, and about 10mg of EVA independent things were measured respectively, and endoergic peak temperature and the amount of endoergic were measured. A testing machine is a product made from Physical science Electrical and electric equipment, and THERMOFLEX. DSC8230 was used. Moreover, in witepsol and the end of progesterone Hara, it measured similarly.

[0074] Per [ DSC ] EVA independent thing was used with what mixed respectively witepsol W-35 and five kinds of EVA (40Y, 45X, 150,250,420) to 9:1, and endoergic peak temperature and the amount of endoergic were measured.

[0075] Drawing 17 is the diagram showing various endoergic peak temperature and amounts of endoergic to an acetic-acid vinyl content of EVA, and, as for endoergic peak temperature and drawing b, drawing a shows the amount of endoergic. In drawing, an axis of ordinate shows peak temperature (degree C) and the amount (cal/g) of endoergic, and an axis of abscissa shows acetic-acid vinyl content % (VA%).

[0076] In an EVA independent (-), endoergic peak temperature fell and the amount of endoergic also decreased as the acetic-acid vinyl content (VA%) increased. In the mixed base agent (**) of 9:1, endoergic peak temperature did not change and the change with the big amount of endoergic was not seen. Since many [ compared with EVA / far ], as for this, the rate of witepsol is considered to seldom have appeared in the result for the effect of EVA.

[0077] On the other hand, as a result of measuring the endoergic peak temperature in the end of progesterone Hara, it was 130.7 degrees C. From this, it was thought on the occasion of preparation of the suppositories by scorification that

there was no decomposition of progesterone.

[0078] 5) Selection drawing 18 of EVA is the diagram showing the burst size of the progesterone at the time of using the basis which mixed various EVA and witepsol. In drawing, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate was eluted. Used EVA is EVA-40Y, and 45X and 150,250,420, and set the mixing ratio of witepsol W-35 and each EVA to 9:1. In addition, it considered as the comparison, and the thing independent [ W-witepsol 35 ] was also doubled and shown.

[0079] All five kinds of burst sizes of the progesterone of 72 hours after were just over or below 35%. All showed sustained-release compared with witepsol independent suppositories having emitted 82.8% of progesterone 72 hours after. However, the difference of the emission from five kinds of mixed suppositories was not seen. This is considered because the difference of the property of EVA did not appear according to there being few contents of EVA in suppositories.

[0080] The mixing ratio of EVA and witepsol was fixed to 1:9, and the reinforcement of the base material to which the class of EVA was changed was measured. In detail, various EVA was added, the cylindrical basis prepared with a diameter of 47mm in the shape of a cylinder was put on the plinth (No.37) for the chip box trial for JIS (box heart), it pushed on witepsol W-35 with the tooth form pusher bar B furnished with a rheometer (No.13), and reinforcement was measured to it. A result is shown in the next table 1.

[0081]

[Table 1]

| | |
|---|---|
| ウィテップゾールW－３５単独 | ２６３±４６ｇ（S．D） |
| EVA ４０Y | ２０５±２８ |
| ４５X | ２６１±２４ |
| １５０ | ３２４±１８ |
| ２５０ | ３１３±３１ |
| ４２０ | １４５±１３ |

[0082] Furthermore, the penetration (pressurization stress) in 40 degrees C (altogether liquefied) was measured using the same basis. In detail, the basis was heated at 40 degrees C, it presupposed that it is liquefied, and the stress (reinforcement) at the time of pressurizing a disk with a diameter of 10mm by pressurization speed 6 mm/min was measured. A result is shown in the next table 2.

[0083]

[Table 2]

| | |
|---|---|
| ウィテップゾールW－３５単独 | 0.20±0 g (S．D) |
| EVA ４０Y | 0.63±0.05 |
| ４５X | 0.47±0.05 |
| １５０ | 7.37±0.09 |
| ２５０ | 299.67±3.68 |
| ４２０ | 76.90±2.21 |

[0084] Although EVA150 and EVA250 showed the high value in Table A, EVA250 is 299.7g and Table B showed the highest extraordinary value compared with other bases.

[0085] On the other hand, although EVA 40Y and 45X was dissolved after an emission trial and within the extraction thimble when the survivability of the basis in an emission trial was compared, EVA150,250,420 remained, with the form of suppositories maintained. It was shown that EVA250 is more useful than the above result as a mixed base agent of suppositories.

[0086] 6) the thermodynamic parameter EVA 250 -- using -- a mixing ratio with witepsol -- 1:9, 1:6, and 1: -- 4, 1:2, and the changed basis were prepared and endoergic peak temperature and the amount of endoergic were measured like said 4. Drawing 19 is the diagram showing change of the endoergic peak temperature at the time of changing a mixing ratio. In drawing, an axis of ordinate shows endoergic peak temperature (degree C), and an axis of abscissa shows EVA

content %. Drawing 20 is the diagram showing change of the amount of endoergic at the time of changing a mixing ratio. In drawing, an axis of ordinate shows the amount (cal/g) of endoergic, and an axis of abscissa shows EVA content %.

[0087] Endoergic peak temperature was seldom correlated with the content of EVA as shown in drawing 19 . However, the amount of endoergic showed the content of EVA, and forward functionality as shown in drawing 20 . From the above result, by changing the content of EVA, it becomes possible to prepare colliquative [ which is a factor in connection with emission of suppositories ], and it is thought that emission of a chief remedy can also be prepared.

[0088] 7) The burst size of the progesterone in the suppositories administration experiment rectum administration to a rabbit and vagina administration was measured. Specifically, the rectum or the vagina of a feminity Japan white rabbit (one groups [ three ]) before and behind the weight of 3.0kg which abstained from food for 24 hours was medicated with suppositories. About 1ml of blood was extracted with time, plasma was isolated preparatively, and the amount of progesterone in plasma was calculated by the radioimmunoassay method using made in the 1st radioisotope lab "the Ith kit II of progesterone."

[0089] the witepsol-EVA mixing suppositories (one each about 0.7g) containing progesterone 50mg were used for suppositories. Furthermore, the rectum of 3 hours after or the condition of a vagina was observed with the naked eye.

[0090] Drawing 21 is the diagram showing the comparison with rectum administration of witepsol suppositories (the amount of progesterone of 50mg), and vagina administration. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows time amount. A difference was hardly seen by rectum administration and vagina administration as shown in drawing.

[0091] Drawing 22 is the diagram showing the result of vagina administration of the witepsol-EVA mixing suppositories by various EVA. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows time amount. Vagina administration of the witepsol-EVA mixing suppositories containing 50mg of progesterone was specifically respectively carried out to the rabbit, and the amount of progesterone in blood was measured. Each witepsol-EVA mixing suppositories were gradual-release-ized as shown in drawing 22 .

[0092] Furthermore, vagina administration of the suppositories (witepsol suppositories) which make a basis only the witepsol W-35 containing progesterone 50mg, and the witepsol-EVA mixing suppositories (mixed suppositories of EVA250 and witepsol) was carried out to the rabbit. Witepsol suppositories were not able to check suppositories in the vagina 1 hour after after administration. However, in the mixed suppositories of witepsol and EVA250, observation of the inside of the vagina 3 hours after after administration observed suppositories slightly.

[0093] Thereby, it was shown in mixed suppositories that there is partial retentivity.

[0094] 8) luteal dysfunction -- charity -- the charity diagnosed as luteal dysfunction in the witepsol independent suppositories containing suppositories administration progesterone 50mg to a desire patient -- the desire patient was medicated at the luteal phase and the progesterone value in blood was calculated. From the acquired value, the corpus luteal hormone index (Luteal Index value) was computed, and it compared with the case of 25mg administration of intramuscular injection.

[0095] Moreover, in 3 of an eucyesis group, a suppositories therapy group, and a non-prescribing a medicine for the patient miscarriage group groups, comparison examination of the amount of progesterone in blood in early gestation was carried out.

[0096] Drawing 23 is the explanatory view showing the corpus luteal hormone index when medicating a luteal phase respectively by the witepsol suppositories and intramuscular injection containing progesterone. namely, a corpus-luteum function -- insufficient charity -- the desire patient was asked for the corpus luteal hormone index in an each luteal phase by the witepsol suppositories administration and the intramuscular injection administration of progesterone 25mg containing progesterone 50mg. A corpus luteal hormone index is expressed as the progesterone blood drug concentration in a luteal phase from the number of corpus-luteum dates.

[0097] Compared with the patient before the therapy of luteal dysfunction, the corpus luteal hormone index became large in both intramuscular injection and the example of suppositories administration as shown in drawing. Suppositories and intramuscular injection showed the almost same value. From the above result, although the doses of progesterone differed, it was shown that suppositories have effectiveness equivalent to intramuscular injection.

[0098] Drawing 24 is the diagram having shown transition of the amount of progesterone in blood of 3 of the eucyesis group in early gestation, the administration group of progesterone content witepsol suppositories, and a non-prescribing a medicine for the patient miscarriage group groups. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows a week. That is, it continued and the amount of progesterone in blood of three groups of the eucyesis group in early gestation, the suppositories therapy group which prescribed progesterone content witepsol suppositories for the patient, and a non-prescribing a medicine for the patient miscarriage group was

measured at nine weeks.

[0099] It was observed that the amount of progesterone in blood becomes almost equivalent to an eucyesis group, and a difference is clearly regarded as a non-prescribing a medicine for the patient miscarriage group by suppositories administration as shown in drawing. The usefulness of the substitution therapy of the progesterone by clinical suppositories was checked from the above thing.

[0100] As mentioned above, the usefulness of the corpus-luteum supplement by suppositories and development of sustained-release mixing suppositories were tried for the purpose of the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery. Moreover, development of a new emission trial of suppositories was also performed.

[0101] Also in addition to it being possible to use the conventional elution test machine, and being cheap, the new emission examining method using the bead and extraction thimble which were performed by this example has the advantage of being able to carry out easily.

[0102] The progesterone content suppositories using the mixed base agent of witepsol and EVA prepared by this example serve as sustained-release compared with witepsol suppositories. Moreover, the mixed suppositories which have sustained-release are also considered to become especially useful suppositories to the progesterone substitution therapy in luteal dysfunction by improving a formula by having shown the useful thing in clinical for the progesterone content suppositories which made witepsol the basis.

[0103]

[Effect of the Invention] The reinforcement which is not dissolved is obtained according to temperature and gradual-release-izing of drug release is possible for what made fusion mixture of witepsol and EVA the basis as this invention was explained above. Furthermore, reservation of galenical pharmacy-stability is possible even if not saved specially in a cool place.

[0104] Moreover, since a burst size increases according to the addition of PEG, what added the polyethylene glycol (it is hereafter described as PEG) as an emission modifier into the fusion mixture of the witepsol of this invention and EVA can control the burst size of an active principle by controlling the addition of PEG.

[0105] There are various drugs, hormone, etc. as an active principle added by the fusion mixture of witepsol and EVA. To be the drugs, hormone, etc. with which a living body is medicated especially with time, and what is necessary is just the drugs, hormone, etc. by which membrane absorption is moreover carried out from the rectum or a vagina wall.

[0106] since especially the thing that added verapamil hydrochloride as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and the verapamil hydrochloride used for the therapy of myocardial infarction -- a basis -- gradually -- softening -- collapsing -- ** -- the verapamil hydrochloride which is not can be gradually prescribed for the patient to the living body.

[0107] Especially in the thing which contains verapamil hydrochloride as an active principle, by using for the witepsol 4 section the basis which added PEG 30% to the fusion mixed base agent of the EVA1 section, the long time of the 1st day or more can be covered, and emission can be maintained.

[0108] Furthermore, since what added progesterone as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis the progesterone which is one of the hormone aiming at the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery, gradually, it follows on collapsing and a basis has softening and the effectiveness that progesterone can be gradually prescribed for the patient to the living body.

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

TECHNICAL FIELD

---

[Industrial Application] About the suppositories applied to the anus or a vagina, especially, this invention does not have to carry out cool place preservation, and relates to suppositories equipped with sustained-release.

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

PRIOR ART

---

[Description of the Prior Art] Usually, suppositories are solid external preparations which mix with a basis equally, cast drugs in a fixed configuration, and apply them to the anus or a vagina, and are external preparations of a half-solid applied to coelomata other than the oral cavity.
[0003] Generally, although suppositories had many things aiming at the local action to hemorrhoids etc., recently, suppositories aiming at a systemic action are increasing. Generally, rectal suppositories are carrying out the cone form or the spindle shape, and although weight 1-3g, die length of 3-4cm, and pessaries are weight 2-4g in a globular form or an ovoid, various advanced types are proposed after that. Amelioration of a configuration is easy to insert, if it inserts, it is hard to jump out and a form which is well stuck to the affected part after insertion is once searched for.
[0004] It roughly divides into suppositories, there are basis form suppositories which blend a drug effect component, an additive, etc. into a basis, and gelatine capsule suppositories which made the gelatine capsule include a paste-like drug solution as them, and basis form suppositories are common.
[0005] It is divided into oleaginous bases, emulsion bases, and water-soluble bases, and as conditions which must be provided as a basis, it melts according to temperature, or softens, or the suppository base of basis form suppositories melts gradually with secretion liquid. Usually, cacao butter, glycerogelatin, macro gall, witepsol, etc. are used as a basis.
[0006] Moreover, if a surfactant is good to emulsion bases, in order that it may close the solubility to the basis of a chief remedy component, and diffusibility to them among basis form suppositories, it may be added by the basis if needed. However, since absorption of a drug may be checked by combination of a surfactant depending on the case, cautions are required.

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

## EFFECT OF THE INVENTION

[Effect of the Invention] The reinforcement which is not dissolved is obtained according to temperature and gradual-release-izing of drug release is possible for what made fusion mixture of witepsol and EVA the basis as this invention was explained above. Furthermore, reservation of galenical pharmacy-stability is possible even if not saved specially in a cool place.

[0104] Moreover, since a burst size increases according to the addition of PEG, what added the polyethylene glycol (it is hereafter described as PEG) as an emission modifier into the fusion mixture of the witepsol of this invention and EVA can control the burst size of an active principle by controlling the addition of PEG.

[0105] There are various drugs, hormone, etc. as an active principle added by the fusion mixture of witepsol and EVA. To be the drugs, hormone, etc. with which a living body is medicated especially with time, and what is necessary is just the drugs, hormone, etc. by which membrane absorption is moreover carried out from the rectum or a vagina wall.

[0106] since especially the thing that added verapamil hydrochloride as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and the verapamil hydrochloride used for the therapy of myocardial infarction -- a basis -- gradually -- softening -- collapsing -- ** -- the verapamil hydrochloride which is not can be gradually prescribed for the patient to the living body.

[0107] Especially in the thing which contains verapamil hydrochloride as an active principle, by using for the witepsol 4 section the basis which added PEG 30% to the fusion mixed base agent of the EVA1 section, the long time of the 1st day or more can be covered, and emission can be maintained.

[0108] Furthermore, since what added progesterone as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis the progesterone which is one of the hormone aiming at the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery, gradually, it follows on collapsing and a basis has softening and the effectiveness that progesterone can be gradually prescribed for the patient to the living body.

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

TECHNICAL PROBLEM

---

[Problem(s) to be Solved by the Invention] By the way, the thing aiming at a systemic action is increasing suppositories as mentioned above, and membrane, such as the rectum which is the main application site, or a vagina, is being improved as a route of administration of a drug. A drug delivery system (DDS) attracts attention from viewpoints, such as the effectiveness of drugs, and safety, in recent years, and many new controlled release pharmaceutical preparation has been developed by the device of dosage forms etc. It doubles with the application purpose also about suppositories, and emission adjustment is being required.

[0008] On the other hand, verapamil hydrochloride is a calcium antagonist, it is administered orally, controls an inflow into the muscle cell of calcium ion (calcium2+), decreases peripheral vascular resistance, and is used for the therapy of angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and myocardial infarction.

[0009] moreover, the corpus-luteum function which progesterone (PRG) causes a failure to formation of pregnancy, and maintenance, and causes infertility, ******, a miscarriage, and a premature delivery -- administration is performed every day by intramuscular injection as an insufficient remedy.

[0010] However, there were problems, such as blood-drug-concentration maintenance by the lapse of the drug effect by the decomposition in the burden to digestive organs, such as the stomach, liver, etc., as a side effect of internal use medicine. Moreover, since self-administration is impossible for intramuscular injection, as for the burden to a patient, it is still larger that there is the need for hospitalization or going to hospital regularly, to be accompanied by the pain, etc.

[0011] In order to compensate the fault of pharmaceutical preparation, such as these internal use medicine and intramuscular injection medicine, current expectation of the development of the pharmaceutical preparation in which self-administration and blood-drug-concentration maintenance are possible is carried out.

[0012] This invention aims at obtaining suppositories equipped with sustained-release [ which can emit a drug effect component gradually ], and obtaining suppositories equipped with sustained-release [ which can adjust the burst size per time amount ].

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

MEANS

---

[Means for Solving the Problem] The sustained-release suppository concerning invention of claim 1 makes a basis fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0014] Moreover, the sustained-release suppository concerning invention of claim 2 adds a polyethylene glycol as an emission regulator into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0015] Furthermore, the sustained-release suppository concerning invention of claim 3 adds verapamil hydrochloride as an active principle into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0016] Moreover, the sustained-release suppository concerning invention of claim 4 adds progesterone as an active principle into the fusion mixture of witepsol and an ethylene-vinyl acetate copolymer.
[0017]

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

OPERATION

---

[Function] Although the witepsol (Witepsol) conventionally used as a suppository base was quickly dissolved in temperature and the drug was emitted, it was found out in what added the ethylene-vinyl acetate copolymer (it is hereafter described as EVA), and was made into the mixed base agent that sustained-release [ good ] is shown.
[0018] Therefore, the reinforcement which is not dissolved is obtained according to temperature and sustained-release [ of drug release ] is possible for what made the basis fusion mixture of the witepsol of this invention, and EVA. Furthermore, even if not saved specially in a cool place, it can save.
[0019] Moreover, since a burst size increases according to the addition of PEG, what added the polyethylene glycol (it is hereafter described as PEG) as an emission regulator into the fusion mixture of the witepsol of this invention and EVA can control the burst size of an active principle by controlling the addition of PEG.
[0020] There are various drugs, hormone, etc. as an active principle added by the fusion mixture of witepsol and EVA. To be the drugs, hormone, etc. with which a living body is medicated especially with time, and what is necessary is just the drugs, hormone, etc. by which membrane absorption is moreover carried out from the rectum or a vagina wall.
[0021] since especially the thing that added verapamil hydrochloride as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis angina pectoris, crown sclerosis (chronic and asymptomatic ischemic heart disease, arteriosclerotic cardiovascular disease), and the verapamil hydrochloride used for the therapy of myocardial infarction -- the inside of the body -- a basis -- softening -- gradually -- gelling -- ** -- the verapamil hydrochloride which is not can be gradually prescribed for the patient to the living body.
[0022] Especially in the thing which contains verapamil hydrochloride as an active principle, by using for the witepsol 4 section the basis which added PEG 30% to the fusion mixed base agent of the EVA1 section, the long time of the 1st day or more can be covered, and emission can be maintained.
[0023] Furthermore, since what added progesterone as an active principle into the fusion mixture of the witepsol of this invention and EVA holds in a basis the progesterone which is one of the hormone aiming at the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery, it can be followed on a basis softening and gelling gradually, and can prescribe progesterone for the patient gradually to the living body.

---

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

---

EXAMPLE

---

[Example]
Verapamil hydrochloride (a sigma company and Lot.70H0897) was used as an example 1. verapamil hydrochloride sustained-release suppository 1 sample chief remedy. As a basis of suppositories, witepsol W-35 and an ethylene-vinyl acetate copolymer (it is hereafter described as EVA) 150,250,420 were used.
[0025] 2) the mixing ratio of the selection witepsol W-35 of optimal EVA, and each of EVA150,250,420 -- 2:1, 3:1, and 4: -- about the basis which carried out fusion mixing as 1 and 6:1, the reinforcement in 25 degrees C and the viscoelasticity in 37 degrees C were measured using the visco-elastic meter (the trade name "FUDOW rheometer" immobilization industrial incorporated company make, model NRM-2002 D-D), and optimal EVA was chosen.
[0026] 2-1) The reinforcement of a basis was measured supposing the handling in the measurement ordinary temperature of the reinforcement in 25 degree C. Drawing 1 is the explanatory view of the adapter of the wedge used for measurement of the reinforcement of a basis. The reinforcement of the basis prepared in 5mm in thickness and width of face of 10mm was measured as shown in drawing. Drawing 2 is the diagram showing the relation between the mixing ratio of EVA in the basis in 25 degrees C, and reinforcement. In drawing, an axis of ordinate shows reinforcement (kg) and an axis of abscissa shows the mixed concentration (%) of EVA.
[0027] The mixed ratio of three kinds of EVA was changed, the mixed dissolution was carried out with witepsol, and the reinforcement of each basis in 25 degrees C was measured as shown in drawing. The level dotted line in drawing shows the reinforcement at the time of witepsol independent. Since suppositories needed to have reinforcement sufficient in ordinary temperature (15-25 degrees C), they were understood that EVA 150 and 250 is the more nearly optimal than drawing.
[0028] 2-2) The viscoelasticity of the basis in 37 degrees C was measured supposing the time of the measurement intrarectal administration of the viscoelasticity in 37 degree C. Drawing 3 is the explanatory view of the adapter for measuring the viscoelasticity of a basis. The viscoelasticity of the basis of the one-side shape of a 10mm cube dipped in the 37-degree C hot bath for 5 minutes was measured using the adapter of a disk form (diameter of 7mm) as shown in drawing.
[0029] Drawing 4 is the diagram showing the relation between the mixing ratio of EVA in the basis in 37 degrees C, and viscoelasticity. In drawing, an axis of ordinate shows visco-elastic degree (kg), and an axis of abscissa shows the mixed concentration (%) of EVA. Change of the elasticity by addition of EVA did not not much have any EVA as shown in drawing.
[0030] In addition, since flexibility was searched for in order to avoid foreign body sensation after insertion of suppositories, in 25%, most flexible EVA250 was chosen by subsequent preparation. Moreover, this basis can maintain the cubical original form, without fusing during heating by hot bath. Therefore, compared with the conventional suppositories, even if it does not carry out cool place preservation, it can fully save.
[0031] 3) the method-of-preparation witepsol W-35 and EVA250 of verapamil hydrochloride sustained-release suppository -- 3:1 and 4: -- verapamil hydrochloride sustained-release suppository was prepared with the fusion method using the basis mixed by 1 and 6:1. It was made to contain 60mg of verapamil hydrochloride in per suppositories at this time.
[0032] After the concrete method of preparation put witepsol W-35 and EVA250 into the beaker, covered on the lap for the food packing made from a polyvinylidene chloride first and carried out the nitrogen purge of the internal air, it was heated for 7 minutes and 30 seconds with the microwave oven. Next, it mixed until it put on the hot plate and became homogeneity using the glass rod so that the temperature of a basis might not fall. After being easy to add verapamil hydrochloride and stirring it to the basis which became homogeneity, it slushed into the metal suppository mold and suppositories (about 1.42g per piece) were prepared.

[0033] 4) It asked for the elution nature of the drug from the elution test suppositories of verapamil hydrochloride sustained-release suppository by ** cylindrical paper filter sampling and the ** basket bead method for having changed the JP rotatory basket method. It carried out using the tester ( model NTR-VS3 by Toyama industrial incorporated company) at rotational-speed 150rpm, the testing-liquid physiological saline of 900ml, and the solution temperature of 37**0.5 degrees C.
[0034] 4-1) Cylindrical-paper-filter-sampling drawing 5 is the explanatory view showing the outline of cylindrical paper filter sampling. The basket (51) used the thing with a diameter [ of 20mm ], and a depth of 30mm used with the JP rotatory basket method as shown in drawing. The extraction thimble (52), and (the Tokyo filter paper firm make, No.84 and the diameter of 20mm) were put in into the basket (51), a physiological saline (54) and suppositories (50) were put in into it, the lid made of silicone rubber (53), and (the thickness of 4mm and the diameter of 18mm) were carried out, and the tester was made to attach and rotate this. 0. 5ml of samples was extracted 5, 1, 3, and 5 or 24 hours after, and the physiological saline of tales doses was filled up.
[0035] 4-2) Using the spectrophotometer (the Jasco Industries make, Ubest-30 mold), the absorbance [ in / for the amount of verapamil hydrochloride to which elution of / in the quantum extraction sample of verapamil / was carried out / 229nm ] was measured, and it computed from the calibration curve (correlation coefficient 1.000) created beforehand. The regression is as follows.
Concentration (mug/ml) = 32.09x absorbance +0.225 [0036] 4-3) Emission nature (1) drawing 6 of verapamil hydrochloride sustained-release suppository is the diagram having shown the result of the emission nature of the drug from the suppositories by cylindrical paper filter sampling. In drawing, an axis of abscissa shows time amount for the rate (rate of emission) (%) to the content of the amount of verapamil hydrochloride to which elution of the axis of ordinate was carried out. This drawing showed that a basis showed sustained-release [ remarkable ] over 24 hours in all ratios.
[0037] Moreover, it turned out that emission nature increases, so that the mixing ratio of witepsol became large. However, the peak price was also 8% (1 or 24 hours after ratio 6:), and that of the rate of drug release 24 hours after a mixed base agent was extremely low as pharmaceutical preparation of verapamil hydrochloride.
[0038] 4-4) Emission nature (2) which is verapamil hydrochloride sustained-release suppository In order to improve elution nature, the polyethylene glycol (it is hereafter described as PEG) 6000 which is a water soluble polymer was added 30% there to the basis which carried out fusion mixing of witepsol W-35 and EVA250 by 4:1. Drawing 7 is the diagram having shown the result of the emission nature of the drug at the time of adding PEG. In drawing, an axis of abscissa shows time amount for the rate of emission of the verapamil hydrochloride to which elution of the axis of ordinate was carried out (%).
[0039] In the case of the ratio 4:1, emission was promoted for 5.4% to 10.4% as shown in drawing. in addition -- the case where PEG is similarly added 30% although not shown in drawing -- the case of a ratio 3:1 -- 2.9% -- 6.6% -- the case of a ratio 6:1 -- 7.6% -- 12.0% -- ** -- the rate of emission was promoted for any ratio about twice [ about ].
[0040] 4-5) In the body, supposing a pressure being applied to suppositories, it examined to the basket bead method pan using the basket bead method per PEG addition suppositories, and the comparison with cylindrical paper filter sampling was performed to it. Drawing 8 is the explanatory view showing the outline of the basket bead method.
[0041] The basket (81) used the thing with a diameter [ of 40mm ], and a depth of 20mm. Suppositories (80) were installed in the horizontal location, two kinds of 30 beads (the product made of nylon, diameter of 3.95mm) were used together, and the bead (83) of B type which sinks the bead (82) of A type which floats in a basket into a physiological saline (84) in 30 pieces (the product made from polypropylene, diameter of 3.95mm) and a basket was performed.
[0042] 5ml of samples was extracted that it is the same as that of cylindrical paper filter sampling, 0.5, 1 and 3, and 5 or 24 hours after, and the physiological saline of tales doses was filled up. Moreover, the quantum of the amount of verapamil hydrochloride to which elution of [ in an extraction sample ] was carried out as well as the above-mentioned was performed.
[0043] Drawing 9 is the diagram having shown the result of the emission nature of the drug of the PEG addition suppositories of cylindrical paper filter sampling and the basket bead method. In drawing, an axis of abscissa shows time amount for the verapamil hydrochloride concentration (emission concentration) (%) to which elution of the axis of ordinate was carried out. Maintaining sustained-release [ which was stabilized by any suppositories of a ratio over 24 hours ] was checked as shown in drawing.
[0044] Moreover, the emission nature in the basket bead method was higher than cylindrical paper filter sampling, and it went up by 4:1 and it went up even to 22.4% by 6:1 26.5% 17.8% by the ratio 3:1. As mentioned above, when adding PEG to the witepsol-EVA basis, it was checked that a burst size is controllable. Therefore, it is thought in accordance with the therapy concentration of various drugs that application is fully effective.

[0045] 5) From the result of the verapamil hydrochloride sustained-release suppository administration experiment elution test to a rabbit, the rabbit was medicated with the verapamil hydrochloride addition suppositories which added PEG 30% to witepsol-EVA mixed stock (4:1), and the absorption experiment by the rabbit was conducted. The amount of suppositories Nakashio acid verapamil was prepared so that 60mg per piece might be contained as well as an elution test. In addition, what added the verapamil hydrochloride of tales doses was prepared for the witepsol independent basis as a comparison.
[0046] Intrarectal administration of the verapamil hydrochloride addition suppositories was specifically carried out to the feminity Japan white rabbit (one groups [ three ]) with a weight of 2.9-3.2kg made to abstain from food for 24 hours, and about 50microl extraction of blood was done from the lug vein 1, 3, and 5 or 24 hours after. The blood drug concentration of the extracted blood was measured using high speed liquid chromatography.
[0047] The measuring method added internal standard matter solution (parahydroxybenzoic acid 2 ethylhexyl methanol solution) 100microl and methanol 200microl to 100micro of blood serums l, applied them to the centrifugal separation machine, performed the deproteinization, and made digestive liquor the sample solution. The device and conditions of high speed liquid chromatography are as follows.
[0048] Pump Shimadzu LC-3A detector Shimadzu The SPD-6A rate of flow 1.0 ml/min column YMC-Pack ODS 150x4.6mmI.D
Mobile phase Phosphate buffer solution: Excitation wavelength of methanol =1:4 detector 278nm [0049] The amount of verapamil hydrochloride was computed by the calibration curve (correlation coefficient 0.9961) created beforehand. The tropic is as follows.
Peak area ratio = 1.5493+9.302x10-3xX (ng/ml)
[0050] Drawing 10 is the diagram showing change of the blood drug concentration of the verapamil hydrochloride when prescribing for the patient the verapamil hydrochloride suppositories which consist of a witepsol independent basis. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, and an axis of abscissa shows time amount. In addition, the doses to Rabbits A, B, and C are 21.7, 19.0, and 21.0 mg/kg, respectively.

[0051] In the witepsol independent used as a suppository base from the former, the transient absorption profile was shown and sustained-release was not accepted as shown in drawing 10 . Cmax in Rabbits A, B, and C They were 195.9 and 129.9 or 199.5mg/ml. In addition, the blood drug concentration of 24 hours high to the abnormalities in Rabbit C is considered to be a certain experiment mistake.
[0052] Drawing 11 is the diagram showing change of the blood drug concentration of the verapamil hydrochloride when medicating a witepsol-EVA mixed base agent (4:1) with the verapamil hydrochloride addition suppositories which added PEG 30%. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, and an axis of abscissa shows time amount.
[0053] In witepsol suppositories, it turns out that the time amount (Tmax) which reaches the maximum drug concentration which was 30min is behind to an average of 3.5 hr(s), or that there is an inclination to maintain higher blood drug concentration 24 hours after as shown in drawing 11 .
[0054] Drawing 12 is the diagram which computed drawing 10 , and averages and standard deviation of 11. In drawing, an axis of ordinate shows the blood drug concentration of verapamil hydrochloride, an axis of abscissa shows time amount, and each plot is the average and standard deviation of each rabbits A, B, and C. It turns out that sustained-release [ Tsuguaki suppositories / using the new basis of this invention shown in drawing 11 ] is shown by drawing 12 . Although it cannot necessarily say that this emission profile is suitable as verapamil hydrochloride pharmaceutical preparation, it is thought that the flexibility in the reinforcement and temperature of these suppositories, firmness, and sustained-release are applicable also to a drug besides future.
[0055] As mentioned above, the following knowledge was acquired as a result of trying the application to the sustained-release suppository by the new basis obtained from the former by carrying out fusion mixing of EVA by the witepsol used as a suppository base.
[0056] In ordinary temperature, since the witepsol-EVA mixed base agent prepared by this example was harder than a witepsol independent, and was not dissolved by temperature but showed moderate flexibility, it also united the sustained-release field and was considered to be useful. Moreover, it succeeded in raising the rate of emission, maintaining sustained-release by adding PEG to a basis in an elution test. When the result of these in vitro experiments was applied to the in vivo experiment using a rabbit, the result which suggests sustained-release similarly was obtained.

[0057] In this example, although verapamil hydrochloride was used as a drug, even if changed into other drugs, it was surmised that it could acquire sustained-release. The property of maintaining emission especially over the long duration

of the 1st day or more is very useful also to development of the pessary which uses hormone etc. as a chief remedy..
[0058] Progesterone was used as an example 2. progesterone suppositories 1 sample chief remedy. Witepsol W-35 and five kinds of EVA (EVA-40Y, 45X, 150,250,420) were used as a basis of suppositories. Moreover, all of reagents, such as other ethanol, used the best article.
[0059] 2) Progesterone content sustained-release suppository was prepared for this with scorification using the basis which mixed the preparation witepsol and EVA of progesterone sustained-release suppository at a rate of 9:1. In addition, the progesterone content suppositories which added progesterone to the witepsol W-35 independent basis were prepared with scorification as control. The amount of progesterone in suppositories set all to 100mg.
[0060] 3) it asked for the elution test of the elution test profit **** sustained-release suppository of progesterone sustained-release suppository by the new emission examining method. As an emission tester, the JP elution test machine (made in the Toyama factory) was used. Drawing 13 is the explanatory view showing the outline of an emission tester. as being shown in drawing -- rotation shaft (131) **** -- propeller (132) it attaches -- having -- further -- rotation shaft (131) Basket (133) surrounded with the network at the tip It is attached.
[0061] It equips with an extraction thimble (the Toyo Roshi Kaisha, Ltd. make, No.84, 20x90mm) (134) into a basket, and is a bead (135) made from plastics with a diameter of 4mm in this. Witepsol suppositories (136) Propeller after putting in and covering with the lid made from silicon (132) Rotation shaft (131) It was made to rotate.
[0062] test fluid (137) ****** -- 5ml of reagents was extracted with time using 900ml of ethanol ********** 30%, and 30% ethanol ********** of tales doses was filled up. The number of beads put in in an extraction thimble was examined by making it change with 50 - 150rpm in the rotational frequency of 0-60 pieces and a basket.
[0063] Using the absorptiometer (the Jasco Industries make, Ubcst-30 mold), the quantum of progesterone measured the absorbance [ in / for test fluid / the wavelength of 248nm ], and asked for it using the calibration curve (y=16.8831x+0.145114 r=0.999839) created beforehand.
[0064] 3-1) Temperature drawing 14 of a physiological saline is the diagram showing the difference of the emission nature of progesterone in case temperature is different. In drawing, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate was eluted. 30 beads were put in with the witepsol suppositories which contain 100mg of progesterone in an extraction thimble 30%, using 900mg of ethanol ********** as test fluid, and it carried out by rotational frequency 150rpm. Temperature was performed at 36 and 37 or 38 degrees C, and compared the emission nature of progesterone.
[0065] Although, as for the burst size of the progesterone 5 hours after emission test initiation, the difference was seldom seen in 37 degrees C and 38 degrees C, in 36 degrees C, the burst size decreased extremely, as shown in drawing.
[0066] From the above result, it is thought in the emission trial of these suppositories that the effect of temperature, i.e., fusion of a basis, influences a burst size greatly. Therefore, temperature of the test fluid in a consecutive trial was made into 37.5**0.5 degrees C near rectal temperature.
[0067] 3-2) The number of beads and engine-speed drawing 15 are the diagrams showing the difference of emission nature in case the number of beads added in an extraction thimble and the engine speed of a basket are different, and, as for 50rpm and drawing b, the engine speed of a basket shows the case of 150rpm for drawing a, as for 100rpm and drawing c. Moreover, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate of each drawing was eluted.
[0068] The number of beads added in an extraction thimble specifically changed the rotational frequency of 0, 10, 30 or 60 pieces, and a basket with 50,100,150rpm, and the emission trial was performed. When engine speeds were 50 and 100rpm as shown in drawing, the effect to the burst size of the number of bead addition was not seen. On the other hand. In 150rpm, the difference was looked at by the burst size with the number of bead addition, and the 30-bead burst size was 78.3%.
[0069] Drawing 16 is the diagram which computed the emission area under the curve (ADT) and the average emission rate (MDT) from the result of drawing 15 , drawing a is an emission area under the curve (ADT), and drawing b is an average emission rate (MDT). In drawing, an axis of ordinate shows an emission area under the curve (ADT) and an average emission rate (MDT), and the axis of abscissa shows the number of beads.
[0070] although ADT showed the peak price in 30 beads as shown in drawing -- MDT -- bead additive-free -- setting -- a high value -- that is, it emitted slowly. Moreover, although emission became quick by addition of a bead, the difference between the numbers of a bead was seldom seen. This is raising an engine speed, and in order for a bead to stir and to make it dissolve more quickly than a basis, it is considered that emission of progesterone becomes quick.
[0071] However, when 60 beads were put in in an extraction thimble, even if it raised the rotational frequency to 150rpm, the burst size did not increase. The movement space of a bead will become narrow and this will be considered

because it becomes impossible to contribute to the dissolution of suppositories, and stirring not much, if suppositories and 60 beads are put in into an extraction thimble.

[0072] From the above result, it became clear by the new emission examining method for having used the above-mentioned JP elution test machine that it is good to carry out by 30 bead additions in an extraction thimble and rotational frequency 150rpm of a basket. leakage and Muranishi of a basis [ like a rotatory basket method ] whose emission examining method of this is -- it is the approach of compensating a fault, like the repeatability in law is inferior, and since the JP elution test machine is used, it is thought that it is cheaper than the rotation dialysis cel method.

[0073] 4) The basis which mixed respectively the measurement witepsol of endoergic peak temperature and the amount of endoergic and five kinds of EVA to 9:1, and about 10mg of EVA independent things were measured respectively, and endoergic peak temperature and the amount of endoergic were measured. A testing machine is a product made from Physical science Electrical and electric equipment, and THERMOFLEX. DSC8230 was used. Moreover, in witepsol and the end of progesterone Hara, it measured similarly.

[0074] Per [ DSC ] EVA independent thing was used with what mixed respectively witepsol W-35 and five kinds of EVA (40Y, 45X, 150,250,420) to 9:1, and endoergic peak temperature and the amount of endoergic were measured.

[0075] Drawing 17 is the diagram showing various endoergic peak temperature and amounts of endoergic to an acetic-acid vinyl content of EVA, and, as for endoergic peak temperature and drawing b, drawing a shows the amount of endoergic. In drawing, an axis of ordinate shows peak temperature (degree C) and the amount (cal/g) of endoergic, and an axis of abscissa shows acetic-acid vinyl content % (VA%).

[0076] In an EVA independent (-), endoergic peak temperature fell and the amount of endoergic also decreased as the acetic-acid vinyl content (VA%) increased. In the mixed base agent (**) of 9:1, endoergic peak temperature did not change and the change with the big amount of endoergic was not seen. Since many [ compared with EVA / far ], as for this, the rate of witepsol is considered to seldom have appeared in the result for the effect of EVA.

[0077] On the other hand, as a result of measuring the endoergic peak temperature in the end of progesterone Hara, it was 130.7 degrees C. From this, it was thought on the occasion of preparation of the suppositories by scorification that there was no decomposition of progesterone.

[0078] 5) Selection drawing 18 of EVA is the diagram showing the burst size of the progesterone at the time of using the basis which mixed various EVA and witepsol. In drawing, an axis of abscissa shows time amount for the concentration of the progesterone in which the axis of ordinate was eluted. Used EVA is EVA-40Y, and 45X and 150,250,420, and set the mixing ratio of witepsol W-35 and each EVA to 9:1. In addition, it considered as the comparison, and the thing independent [ W-witepsol 35 ] was also doubled and shown.

[0079] All five kinds of burst sizes of the progesterone of 72 hours after were just over or below 35%. All showed sustained-release compared with witepsol independent suppositories having emitted 82.8% of progesterone 72 hours after. However, the difference of the emission from five kinds of mixed suppositories was not seen. This is considered because the difference of the property of EVA did not appear according to there being few contents of EVA in suppositories.

[0080] The mixing ratio of EVA and witepsol was fixed to 1:9, and the reinforcement of the base material to which the class of EVA was changed was measured. In detail, various EVA was added, the cylindrical basis prepared with a diameter of 47mm in the shape of a cylinder was put on the plinth (No.37) for the chip box trial for JIS (box heart), it pushed on witepsol W-35 with the tooth form pusher bar B furnished with a rheometer (No.13), and reinforcement was measured to it. A result is shown in the next table 1.

[0081]

[Table 1]

| | |
|---|---|
| ウィテップゾールW－３５単独 | ２６３±４６ｇ（S．D） |
| EVA　４０Y | ２０５±２８ |
| ４５X | ２６１±２４ |
| １５０ | ３２４±１８ |
| ２５０ | ３１３±３１ |
| ４２０ | １４５±１３ |

[0082] Furthermore, the penetration (pressurization stress) in 40 degrees C (altogether liquefied) was measured using

the same basis. In detail, the basis was heated at 40 degrees C, it presupposed that it is liquefied, and the stress (reinforcement) at the time of pressurizing a disk with a diameter of 10mm by pressurization speed 6 mm/min was measured. A result is shown in the next table 2.

[0083]

[Table 2]

| | |
|---|---|
| ウィテップゾールW－３５単独 | 0.20±0 g (S. D) |
| EVA 40Y | 0.63±0.05 |
| 45X | 0.47±0.05 |
| 150 | 7.37±0.09 |
| 250 | 299.67±3.68 |
| 420 | 76.90±2.21 |

[0084] Although EVA150 and EVA250 showed the high value in Table A, EVA250 is 299.7g and Table B showed the highest extraordinary value compared with other bases.

[0085] On the other hand, although EVA 40Y and 45X was dissolved after an emission trial and within the extraction thimble when the survivability of the basis in an emission trial was compared, EVA150,250,420 remained, with the form of suppositories maintained. It was shown that EVA250 is more useful than the above result as a mixed base agent of suppositories.

[0086] 6) the thermodynamic parameter EVA 250 -- using -- a mixing ratio with witepsol -- 1:9, 1:6, and 1: -- 4, 1:2, and the changed basis were prepared and endoergic peak temperature and the amount of endoergic were measured like said 4. Drawing 19 is the diagram showing change of the endoergic peak temperature at the time of changing a mixing ratio. In drawing, an axis of ordinate shows endoergic peak temperature (degree C), and an axis of abscissa shows EVA content %. Drawing 20 is the diagram showing change of the amount of endoergic at the time of changing a mixing ratio. In drawing, an axis of ordinate shows the amount (cal/g) of endoergic, and an axis of abscissa shows EVA content %.

[0087] Endoergic peak temperature was seldom correlated with the content of EVA as shown in drawing 19 . However, the amount of endoergic showed the content of EVA, and forward functionality as shown in drawing 20 . From the above result, by changing the content of EVA, it becomes possible to prepare colliquative [ which is a factor in connection with emission of suppositories ], and it is thought that emission of a chief remedy can also be prepared.

[0088] 7) The burst size of the progesterone in the suppositories administration experiment rectum administration to a rabbit and vagina administration was measured. Specifically, the rectum or the vagina of a feminity Japan white rabbit (one groups [ three ]) before and behind the weight of 3.0kg which abstained from food for 24 hours was medicated with suppositories. About 1ml of blood was extracted with time, plasma was isolated preparatively, and the amount of progesterone in plasma was calculated by the radioimmunoassay method using made in the 1st radioisotope lab "the Ith kit II of progesterone."

[0089] the witepsol-EVA mixing suppositories (one each about 0.7g) containing progesterone 50mg were used for suppositories. Furthermore, the rectum of 3 hours after or the condition of a vagina was observed with the naked eye.

[0090] Drawing 21 is the diagram showing the comparison with rectum administration of witepsol suppositories (the amount of progesterone of 50mg), and vagina administration. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows time amount. A difference was hardly seen by rectum administration and vagina administration as shown in drawing.

[0091] Drawing 22 is the diagram showing the result of vagina administration of the witepsol-EVA mixing suppositories by various EVA. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows time amount. Vagina administration of the witepsol-EVA mixing suppositories containing 50mg of progesterone was specifically respectively carried out to the rabbit, and the amount of progesterone in blood was measured. Each witepsol-EVA mixing suppositories were gradual-release-ized as shown in drawing 22 .

[0092] Furthermore, vagina administration of the suppositories (witepsol suppositories) which make a basis only the witepsol W-35 containing progesterone 50mg, and the witepsol-EVA mixing suppositories (mixed suppositories of EVA250 and witepsol) was carried out to the rabbit. Witepsol suppositories were not able to check suppositories in the vagina 1 hour after after administration. However, in the mixed suppositories of witepsol and EVA250, observation of the inside of the vagina 3 hours after after administration observed suppositories slightly.

[0093] Thereby, it was shown in mixed suppositories that there is partial retentivity.
[0094] 8) luteal dysfunction -- charity -- the charity diagnosed as luteal dysfunction in the witepsol independent suppositories containing suppositories administration progesterone 50mg to a desire patient -- the desire patient was medicated at the luteal phase and the progesterone value in blood was calculated. From the acquired value, the corpus luteal hormone index (Luteal Index value) was computed, and it compared with the case of 25mg administration of intramuscular injection.
[0095] Moreover, in 3 of an eucyesis group, a suppositories therapy group, and a non-prescribing a medicine for the patient miscarriage group groups, comparison examination of the amount of progesterone in blood in early gestation was carried out.
[0096] Drawing 23 is the explanatory view showing the corpus luteal hormone index when medicating a luteal phase respectively by the witepsol suppositories and intramuscular injection containing progesterone. namely, a corpus-luteum function -- insufficient charity -- the desire patient was asked for the corpus luteal hormone index in an each luteal phase by the witepsol suppositories administration and the intramuscular injection administration of progesterone 25mg containing progesterone 50mg. A corpus luteal hormone index is expressed as the progesterone blood drug concentration in a luteal phase from the number of corpus-luteum dates.
[0097] Compared with the patient before the therapy of luteal dysfunction, the corpus luteal hormone index became large in both intramuscular injection and the example of suppositories administration as shown in drawing. Suppositories and intramuscular injection showed the almost same value. From the above result, although the doses of progesterone differed, it was shown that suppositories have effectiveness equivalent to intramuscular injection.
[0098] Drawing 24 is the diagram having shown transition of the amount of progesterone in blood of 3 of the eucyesis group in early gestation, the administration group of progesterone content witepsol suppositories, and a non-prescribing a medicine for the patient miscarriage group groups. In drawing, an axis of ordinate shows the blood drug concentration of progesterone, and an axis of abscissa shows a week. That is, it continued and the amount of progesterone in blood of three groups of the eucyesis group in early gestation, the suppositories therapy group which prescribed progesterone content witepsol suppositories for the patient, and a non-prescribing a medicine for the patient miscarriage group was measured at nine weeks.
[0099] It was observed that the amount of progesterone in blood becomes almost equivalent to an eucyesis group, and a difference is clearly regarded as a non-prescribing a medicine for the patient miscarriage group by suppositories administration as shown in drawing. The usefulness of the substitution therapy of the progesterone by clinical suppositories was checked from the above thing.
[0100] As mentioned above, the usefulness of the corpus-luteum supplement by suppositories and development of sustained-release mixing suppositories were tried for the purpose of the therapy of the infertility by luteal dysfunction, ******, a miscarriage, and a premature delivery. Moreover, development of a new emission trial of suppositories was also performed.
[0101] Also in addition to it being possible to use the conventional elution test machine, and being cheap, the new emission examining method using the bead and extraction thimble which were performed by this example has the advantage of being able to carry out easily.
[0102] The progesterone content suppositories using the mixed base agent of witepsol and EVA prepared by this example serve as sustained-release compared with witepsol suppositories. Moreover, the mixed suppositories which have sustained-release are also considered to become especially useful suppositories to the progesterone substitution therapy in luteal dysfunction by improving a formula by having shown the useful thing in clinical for the progesterone content suppositories which made witepsol the basis.

---

[Translation done.]